We Claim:

1. A soluble fusion protein comprising recombinant Notch protein fused to the C--terminus of a NusA protein sequence.

2. The soluble fusion protein of claim 1, wherein said recombinant Notch protein comprises the S3 cleavage site of Notch.

3. The soluble fusion protein of claim 1, wherein said recombinant Notch protein is a vertebrate Notch protein.

4. The soluble fusion protein of claim 1, wherein said recombinant Notch protein is an invertebrate Notch protein.

5. The soluble fusion protein of claim 1, wherein said recombinant Notch protein is derived from mouse Notch protein having the sequence of SEQ ID NO:5.

6. The soluble fusion protein of claim 1, wherein said recombinant Notch protein comprises amino acids 1703 through 1860 of mouse Notch protein.

7. The soluble fusion protein of claim 1, further comprising a C-terminal His-tag.

8. The soluble fusion protein of claim 1, further comprising a C-terminal Flag-tag.

9. A polynucleotide comprising a nucleotide sequence that encodes a fusion protein according to claim 1.

10. A polynucleotide sequence that encodes a fusion protein of claim 1, wherein said polynucleotide sequence comprises a sequence set forth in SEQ ID NO:1.

11. An expression vector comprising a polynucleotide of claim 9.

12. The expression vector of claim 11, wherein said polynucleotide is operably linked to a promoter to promote expression of the protein encoded by the polynucleotide in a host cell.

13. A recombinant host cell transformed or transfected with a polynucleotide of claim 9.

14. A recombinant host cell transformed or transfected with an expression vector of claim 11.

15. A method of producing a solubilized Notch protein, said method comprising preparing a fusion protein wherein the said Notch protein is fused to the C-terminus of a NusA protein.

16. The method of claim 15, wherein said method comprises a recombinant production of said fusion protein, said method comprising:

a. preparing an expression construct comprising a nucleic acid that encodes a fusion protein comprising a Notch protein containing the amino acids of the S3 cleavage site of Notch linked at the C-terminus of a NusA protein;

b. transforming a host cell with said expression construct under conditions that facilitate the expression of said fusion protein; and

c. growing said transformed host cell in culture.

17. The method of claim 16, further comprising isolating said fusion protein from said transformed host in culture.

18. The method of claim 15, wherein said method comprises producing said fusion protein through chemical protein synthesis.

19. The method of claim 16, wherein said Notch protein comprises amino acids 1703 through 1860 of mouse Notch protein.

20. An *in vitro* method of assaying for γ-secretase mediated ε cleavage (1743/1744) of Notch protein comprising:

a. contacting a first composition comprising a mammalian γ-secretase complex or biologically active fragment thereof, with a second compositions comprising a fusion protein according to claim 1; and

b. measuring cleavage of the fusion protein.

21. An *in vitro* method of screening for modulators of γ-secretase mediated ε cleavage (1743/1744) of Notch protein, comprising the steps of:

(a) contacting a first composition comprising a mammalian γ-secretase complex or biologically active fragment thereof, with a second compositions comprising a fusion protein according to claim 1 in the presence and in the absence of a putative modulator compound; and

(b) measuring cleavage of the fusion protein in the presence and in the absence of a putative modulator compound; and

(c) identifying modulators which modulate the γ-secretase mediated cleavage of said fusion protein;

wherein a putative modulator compound produces a difference in γ-secretase cleavage in step (b).

22. The method of claim 20, wherein the γ-secretase complex of the first composition comprises a membrane fraction purified and isolated from mammalian cells or cells transformed or transfected with expression constructs comprising nucleotide sequences that encode the γ-secretase complex.

23. The method of claim 20, wherein said fusion protein is a solubilized Notch protein prepared according to any one of claims 15 through 19.

24. The method of claim 21, wherein the putative modulator compound modulates the γ-secretase cleavage of APP.

25. The method of claim 21, wherein the putative modulator compound inhibits the γ-secretase cleavage of APP to a greater extent than γ-secretase cleavage of Notch protein.

26. A method of producing a substrate for a γ-secretase assay comprising growing a host cell of claim 13 in a manner allowing expression of said fusion protein.

27. The method of claim 26, further comprising purifying said polypeptide.

28. The method of claim 26, wherein said host cell is selected from the group consisting of a mammalian host cell, a bacterial host cell and a yeast host cell.

29. The method of claim 28, wherein the cell is a Hela cell, a human embryonic kidney cell line 293 cell, a fibroblast, or a CHO cell.

30. A method of producing a substrate for a γ-secretase assay comprising growing a host cell of claim 14 in a manner allowing expression of said polypeptide.

31. The method of claim 30, further comprising purifying said polypeptide.

32. The method of claim 31, wherein said host cell is selected from the group consisting of a mammalian host cell, a bacterial host cell and a yeast host cell.

33. The method of claim 32, wherein the cell is a Hela cell, a human embryonic kidney cell line 293 cell, a human embryonic kidney cell line 293 cell, a fibroblast, or a CHO cell.

34. A kit for performing a γ-secretase assay comprising a γ-secretase substrate comprising a fusion protein according to claim 1.

35. The kit of claim 34, further comprising reagents for detecting the cleavage of said fusion protein.

36. A fusion protein comprising a NusA polypeptide fused to a Notch polypeptide comprising between 90 to 95% sequence identity with a NusA sequence of SEQ ID NO:14, wherein the Notch polypeptide comprises the transmembrane domain of Notch, and wherein the fusion protein is soluble in an aqueous solution.

37. A method for screening for a selective inhibitor of γ-secretase processing of amyloid precursor protein (APP), comprising:

a) providing a test compound which inhibits γ-secretase mediated cleavage of a polypeptide comprising an APP gamma secretase site; and

b) measuring gamma secretase cleavage of a fusion protein according to claim 1 in the presence and absence of the test compound;

wherein a test compound that preferentially inhibits gamma secretase cleavage of said polypeptide compared to cleavage of said fusion protein is a selective inhibitor of gamma secretase processing of APP.

38. A selective inhibitor identified by the method of claim 37.

39. A method of modulating γ-secretase activity *in-vivo* comprising a step of administering a selective inhibitor of claim 37 to a mammal in an effective amount to modulate γ-secretase activity in cells of said mammal.

40. A pharmaceutical composition comprising a selective inhibitor of claim 38 and a pharmaceutically acceptable carrier.

41. A method of treating a disease or condition characterized by an abnormal γ-secretase activity comprising administering to a subject in need of treatment a pharmaceutical composition of claim 40.

42. A use of a selective inhibitor identified according to the method of claim 37 in the manufacture of a medicament for the treatment of Alzheimer's disease.